35 USC §102(b)

The Examiner has rejected claims 1-3, 5-6, 20-21 and 23-25 as being anticipated by Lee *et al.* (WO 98/43647) ("Lee") alone, or in view of Borchelt. Claims 1 and 20 have been amended to recite that the dose of estrogen does not affect soluble APP levels. As discussed during the interview, Lee teaches administration of high dose estrogen (superphysiological doses) that inhibit production of APP protein. For example, Lee states that "[i]t has now been discovered that APP expression can be regulated by lipophilic hormones..., [t]hus these substances can be used to prevent APP overexpression in brain cells." (Lee, page 6, lines 10-14)(emphasis added). Lee sets out to modulate "... expression, production, or formation of amyloid precursor protein (APP) in a subject ..." (Lee, page 6, lines 24-25). According to Lee, "APP expression can be regulated by lipophilic hormones that interact with cytosolic or nuclear receptors[,]" (Lee, page 7, lines 24-25), e.g., estrogenic compounds such as 17β-estradiol. (Lee, page 6, lines 15-16 and page 7, lines 26-30). Furthermore, under the high concentration conditions described in Lee, "...estrogenic compounds reduce APP holoprotein levels by decreasing APP synthesis[,]" and it is this reduction in APP holoprotein that is expected to reduce neurotoxicity or neurodegeneration. (Lee, page 8, lines 6-11). The decrease in APP holoprotein is associated with decreased production of APP mRNA. (Lee, page 9, lines 4-7).

In contrast to Lee, the present invention is based on the discovery that physiologic levels of estrogen compounds, which do not affect soluble APP levels, instead affect processing of APP into β-amyloid (Aβ), and especially the more neurotoxic Aβ-42.

The Examiner's basis for rejection appears to result from a fundamental misunderstanding that the lower, physiological dose of estrogen of the present invention does not affect APP, but rather it affects the processing of APP into amyloid. This is a distinction with a difference. Lee clearly distinguishes the ability to reduce APP expression from methods that affect APP processing: see, e.g., page 3, lines 22-23 - "...none of these studies discloses or suggest that the administration of NSDAs *prevents* the overproduction of APP" (emphasis in the original), page 4, lines 10-12 - "...Buxbaum *et al.* made no mention, teaching or suggestion that the step preceding the processing of APP, that is expression, production, or formation of APP, itself, can be at all affected by select groups of substances..." (emphasis added); "page 4, lines 26-27 - "In contrast to the above studies, the present invention, as disclosed herein, concerns the expression, formation, or synthesis of APP." APP is the precursor of Aβ. Lee contrasts this result with results that show increases in the level of soluble APP but no change in the level of APP holoproteins. (Lee, page 8, lines 18-24). While Lee's high dose estrogen inhibits production of the precursor, the present invention concerns modulating production of the product, independently of production of precursor. Indeed, Lee teaches that APP has direct neurotoxic effects (see p. 5, lines

20-24; page 7, lines 3-8; page 8, lines 9-11).

To anticipate a claim, a reference "must disclose every element of the [] claim and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.*, 37 USPQ 2d 1618, 1624 (Fed. Cir. 1996). The limitations must be expressly or inherently present in the single prior art reference. *In re Robertson*, 49 USPQ 2D 1949, 1950 (Fed. Cir. 1999). An inherent limitation is one that is necessarily present; invalidation based on inherency is not established by "probabilities or possibilities." *Scaltch, Inc. v. Retch/Tetra, LLC*, 51 USPQ 2D 1055, 1059 (Fed. Cir. 1999).

The mistake the Examiner makes here is to view general statements in Lee about doses of compounds independently of the required effect. The Examiner's rejection fails to take account of the widely varying compounds recited by Lee as having the ability to inhibit APP production, including, in addition to estrogens, thyroid hormones, human growth hormones, insulin, etc. (Lee, page 10, lines 29-31). Even the dose of any given estrogen needed to achieve inhibition of APP expression can vary compared to another estrogen because of intrinsic activity of the estrogen compounds. What Lee requires, in distinction to the present invention, is that the amount of estrogen compound inhibits APP production. This is in contrast to lower amounts of estrogens that appear to account for the lack of effect on APP holoprotein. (See Lee, page 8, lines 26-28). There is simply no indication in Lee that these wide dosage ranges apply to every possible compound, which is why Lee specifically

teaches that the effective amount is "...a sufficient amount of the compound to treat or alleviate the negative effects of a neurological disorder or neurodegenerative disease stemming from an increase in the level of expression, production or formation of [APP] ....", i.e., inhibit APP. (Lee, page 13, lines 22-26). Lacking any other guidance from the specification other than the required functional affect (Id.), and the need to achieve super physiological levels of estrogen for inhibition of APP holoprotein synthesis (see page 8, lines 26-28, and the Examples, as discussed in the previous amendment and during the interview), Lee cannot inherently disclose the limitations of the claimed invention.

The claims as amended clearly distinguish the present invention from Lee by Lee's express teaching. (The claims also distinguish the *in vivo* invention from the *in vitro* results of Jaffe, which Lee discusses at page 8, lines 10-29).

Since Lee at no time suggests affecting processing of APP, and indeed teaches administration of compounds that inhibit production of APP prior to its processing, it is inconceivable that the reference could somehow implicate the ratio of Aβ42 to Aβ40, much less provide any teaching of altering that ratio. Borchelt does not establish subject matter inherent to Lee. (As discussed below, it also fails to make this subject matter obvious.)

Thus, the '647 reference cannot anticipate claims 1 and 20 as amended. It is respectfully requested that the Examiner allow the amendments and remove the 35 USC §102(b) rejections relating to the claims. In addition, if the amendment to

claims 1 and 20 are allowed by the Examiner, it is respectfully requested that the Examiner remove the 35 USC §102(b) rejections of claims 2-3, 5-6, 21, and 23-25 which depend from either claim 1 or 20.

35 USC §103

Claims 1-6, 15, and 18-30 are rejected as obvious over Lee alone and further in combination with Borchelt. The Examiner maintains that Lee inherently teaches the claimed invention on the basis that Lee's inhibition of APP production somehow inherently relates to Aβ42 to Aβ40 formation. The examiner further contends that it would have been obvious to one skilled in the art at the time of the invention to combine Lee and Borchelt to measure the amounts and/or ratio of Aβ42 to Aβ40 to determine whether a compound is effective at reducing these levels or ratio.

These rejections are respectfully traversed, and reconsideration is requested. For the reasons set forth above with respect to the anticipation rejections, Lee teaches a different dosage of estrogen to achieve a different effect: inhibition of APP production. The present claims are directed to methods that employ doses of estrogenic compounds that do not affect APP levels, but do affect Aβ levels, and particularly (and surprisingly) the ratio of Aβ42 to Aβ40.

The citations in Lee that the Examiner alleges suggest the invention do nothing of the kind: they all relate to inhibition of APP production. Lee does not suggest that Aβ levels correlate with APP, and in fact proposes that APP is directly

neurotoxic (see Lee, p. 5, ll. 20-24 and p. 7, ll. 3-6; Lee states that "'APP overexpression' [means] any activity that is exerted in the nucleus of a eukaryotic cell that ultimately gives rise to expression, production, or formation of APP in a subject ...", thus excluding the processing of APP to form Aβ as practicing the technology). Lee does not provide any motivation to modify the high concentrations of estrogen needed to inhibit APP expression to the lower concentrations that modulate Aβ levels without inhibiting APP production, and specifically distinguishes such low levels. Thus, only hindsight reconstruction gleaned from the specification of the present application yields the motivation required to modify Lee, and such hindsight reconstruction is not permissible. The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure" [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

With respect to the rejection over the combination of Lee and Borchelt, neither reference contains any motivation to combine the two. Lee only teaches lowering APP levels in brain cells cultured *in vitro* with astronomical levels of estradiol. Borchelt show no correlation between APP expression and the ratio of Aβ42 to Aβ40. Borchelt teach that familial Alzheimer's Disease-linked presenilin 1 variants elevate Aβ1-42/Aβ1-40 ratio *in vitro* and *in vivo*, which is an APP processing event completely

independent of APP expression. As admitted by the Examiner, Lee does not specifically teach a role for the ratio of Aβ42 to Aβ40 in the pathogenesis of Alzheimer's Disease. Since Lee does not specifically teach a role for the ratio of Aβ42 to Aβ40 in the pathogenesis of Alzheimer's Disease and Borchelt does not provide a link between APP expression and the ratio of Aβ42 to Aβ40 in the pathogenesis of Alzheimer's Disease, neither reference provides the needed motivation to combine them. In fact, Lee teaches away from such a combination by emphasizing the apparent neurotoxicity of APP (the precursor to amyloid peptide).

Accordingly, Applicants respectfully request withdrawal of these rejections.

Claims 1-30 are rejected as obvious over Lee in combination with Borchelt and in further combination with Simpkins. Claims directed to orchidectomy are further rejected in view of Williams and Stancel (Goodman and Gilman's 1996). The Examiner relies on Simpkins for teaching ovariectomy as a model for postmenopausal changes and Williams and Stancel for teaching the synthesis of estradiol from testosterone. The Examiner concludes that it would have been obvious to one skilled in the art at the time of the invention to combine Lee, Borchelt and Simpkins to utilize ovariectomy as a model for postmenopause, and to determine the capacity of a drug to treat Alzheimer's Disease through measurement of amounts and/or ratios of Aβ42 to Aβ40.

Applicants respectfully traverse this rejection, and reconsideration is requested.

The previous arguments regarding Lee and Borchelt apply to these further rejections. Nothing in Lee provides any suggestion or motivation to look at the level of Aβ, much less the ratio of Aβ42 to Aβ40 for therapy or to identify a compound as a candidate for treating Alzheimer's Disease. Simpkins and Williams and Stancel do not suggest or disclose subject matter missing from Lee and Borchet to arrive at the present invention. Thus, obviousness does not obtain.

It is specifically worth noting that the method of evaluation claims (7-13 and 14-19) are not suggested, much less taught, in the references taken alone or in combination. The examiner has generally extrapolated from incorrect assumptions about Lee that are clearly based on the instant specification rather than on the objective teaching of the reference as a whole, and to this has tacked on references that purport to suggest features of the claimed assays of claims 7-19. At best, the references taken in combination might suggest an assay system for evaluating compounds that inhibit APP production, but they in no way suggest the orchiectomized models and detection of Aβ as claimed.

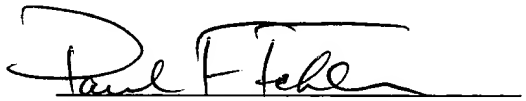
Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of this application. These amendments are necessary to place the claims in condition for allowance. These claims clearly meet the statutory criteria for patentability. The Patent and Trademark Office has had an opportunity to examine all issues with respect to the patentability of the claims, and the applicants and the Examiner have done everything possible to arrive at patentable subject matter. Allowance of the claims is earnest solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Suzana PETANCESKA; Sam GANDY; Donald E. FRAIL

Serial No.: 09/695,446 Art Unit: 1615

Confirmation No.: 2608

Filed: 10/24/00 Examiner:

For: METHODS FOR IDENTIFYING AND USING AMYLOID-INHIBITORY COMPOUNDS

MARKED-UP VERSION OF CLAIMS

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

January 3, 2003

Sir:

1. (Amended) A method for reducing a level of amyloid-β (Aβ) peptides *in vivo*, which method comprises administering an Aβ level reducing dose of an estrogen compound to an animal, wherein the animal has an increased level of Aβ, and wherein

the dose of the estrogen compound does not affect soluble APP levels.

20. A method for delaying or reducing the likelihood of, or ameliorating, a disease or disorder associated with amyloidosis, which method comprises administering an Aβ level reducing dose of an estrogen compound to a subject who has an increased risk for developing or shows a symptom of the disease or disorder associated with amyloidosis, wherein the dose of the estrogen compound does not affect soluble APP levels.

Respectfully submitted,

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